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THE EFFECT OF CROSSING NERVES TO ANTAGONISTIC MUSCLES IN THE HIND LIMB OF THE RAT

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When nerves to limb muscles are forced by operative measures to activate opposing muscles in amphibians, no corresponding disturbance results in the response pattern of the limb muscles (Weiss, '36). Contrary to the view that specific connections between nerve centers and end organs are important in determining the pattern of response, the muscles or limbs so operated contract normally in timing and in intensity regardless of the experimental distortion of their nerve connections. It has been demonstrated further that this return to normal function after crossing of limb nerves in amphibians is not the result of reeducation or of any kind of automatic reflex adjustment (Weiss, '37).

The only tenable explanation of the phenomenon yet suggested is that offered by Weiss himself in terms of modulation of nerve by muscle. When nerve fibers growing out in ontogenetic development make contact with peripheral organs, they are presumably induced by those end organs to undergo a further cell differentiation according to the specific biochemical properties of the end organ. Nerves to different muscles thus become differentiated qualitatively from each other. When a nerve is severed from its muscle and forced to

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regenerate into a foreign muscle, the nerve cells under the influence of the new muscle, undergo a process of cell modulation losing the specific properties induced by the original muscle and acquiring those specific to the new muscle. These specific properties of motor nerves result in selective sensitivity of the nerves of the various muscles to different central excitatory agents. According to the Resonance Principle this selective sensitivity rather than the anatomical connections in the ventral horn, links the individual muscles with their respective central activators. Normal function thus reappears after experimental disarrangement of the peripheral nerve connections as soon as the nerves are modulated by the muscles into which they regenerate. Evidence has been presented that nerves undergo these muscle-specific changes also in embryonic stages of human development (Weiss, '35).

Apparent recovery of normal function after nerve crossing in birds and mammals has in the past been attributed to reeducation or to automatic reflex regulation without testing for other possible factors such as modulation of nerve by muscle. Flourens (1842) crossed the medial and ulnar nerves in the fowl. Rawa (1885) crossed the peroneal and tibial nerves in rabbits, cats, dogs, and pigs. Osborne and Kilvington ('10) crossed the peroneal and tibial nerves in dogs. These investigators all report a restoration of normal function and attribute it to reeducation. Barron ('34) in summarizing the literature concludes that the crosses between spinal nerves have been more successful than those between cranial nerves in being followed by a complete independence of the movements of the muscle groups involved. He made anastomoses between fore and hind limb nerves in the rat and reported that a gradual dissociation of movement occurred as the result of a learning process. Kennedy ('14) after crossing flexor and extensor nerves in the front leg of the dog, states that recovery occurred without any evidence of a training period and that it was probably due to an immediate reflex adjustment to the altered periphery rather than to learning. Although the numerous clinical reports are somewhat controversial, the predominating opinion in neuro-surgery seems to be that the crossing of limb nerves in human patients results in a corresponding distortion of sensation or response which can be corrected in time by reeducation provided there are not numerous axon bifurcations to non-synergic muscles or to receptors of different modality.

These reports imply a plasticity of the nerve centers that is directly at variance with the results of muscle transposition in rats (Sperry, '40). When flexor and extensor muscles of the hind foot of 50-day-old rats are transposed, a reversal of foot movement follows which persists permanently without the slightest corrective modification. Even after amputation of the front legs and 8 months of special training, the foot action remains unalterably reversed. In view of the fact that foot coordination in these cases proved completely refractory to reeducation, it seems questionable that the ready restoration of apparently normal foot function following nerve crosses in rabbits, cats, dogs, and pigs could actually have been due to learning or reflex regulation. Persistence of the correction in foot movement after cord transection in Osborne and Kilvington's dogs suggests, in itself, that the adjustment was due to some factor other than reeducation, because spinal conditioning has never been conclusively demonstrated elsewhere. Modulation of nerve by muscle is such another factor that would result in recovery of normal function. In amphibians an age difference has been demonstrated; modulation occurs quickly in larval stages but may require as long as several months in older animals (Weiss, '36). A corresponding slow modulation of crossed nerves in post-embryonic mammals would be practically indistinguishable in effect from reeducation.

To date no study has been undertaken to determine for certain whether or not such a modulation process occurs. In the present experiments nerves were crossed in the hind limb of the rat to the same set of muscles which was used previously in muscle transposition for the purpose of (1) comparing the functional effects of nerve crossing and muscle

transposition under similar conditions, and (2) discovering whether the limb nerves of postnatal mammals have become irreversibly determined or are still capable of undergoing muscle-specific changes on regeneration into foreign muscles.

METHOD

A reversal of hind foot movement was produced by crossing nerves to flexor and extensor muscles of the shank. In the previous investigations of other authors on the crossing of limb nerves, large compound nerve trunks have been employed containing fibers to several different groups of muscles as well as a large number of cutaneous and other sensory components. Reeducation was favored and general confusion avoided in the present work by isolating and crossing the pure individual branches to single muscles. All remaining shank muscles, whose nerves were not crossed, were excised. This clarifies, for study, the action of the test muscles and also eliminates reflex inhibition of reeducation by the continued action of shank muscles with normal innervation.

Because both modulation and reeducation result in restoring normal limb function after nerve crossing, critical conditions were established to separate the two factors so that one could clearly tell of any adjustment in function that occurred whether it was due to modulation or to reeducation: Correction of reversed foot movement following the crossing of nerves, when it had been shown not to follow the transposition of the muscles supplied by those nerves, would, in itself, suggest that some factor other than reeducation was responsible. Spinal cord transection should abolish the adjustment if due to learning, but not if due to modulation. Furthermore, by first crossing the nerves and then transposing those muscles supplied by the crossed nerves, a crucial test situation was established under the conditions of which modulation could not possibly be mistaken for reeducation. Foot movement in normal phase is the immediate result on recovery from such a double operation (see Sperry, '40). Subsequent modulation of nerve by muscle would have to show up as a shift from

normal to reversed action which could hardly be interpreted as reeducation.

OPERATION

The nerve branch to the soleus muscle, a plantar flexor, was dissected out carefully back to its emergence from the tibial trunk. The nerve was then cut distally next to the muscle, pulled anteriorly, and inserted into the anterior tibial muscle, a dorsi-flexor, after the original nerve to that muscle had been severed. Similarly, the distal cut end of the nerve to the extensor digitorum longus muscle, a dorsi-flexor, was pulled posteriorly and inserted into the medial gastrocnemius muscle, a plantar flexor, after its original nerve had been severed.

All other shank muscles, whose nerves had not been crossed, were excised. The loose ends of the original nerves to the intact muscles and those of the excised muscles were ligated with fine silk thread and tied to tissues away from the intact muscles to prevent undesired regeneration. The nerves were inserted in the muscles directly at the motor point in an attempt to bring the cut end of the foreign nerve into contact with the distal stump of the original nerve whose degenerating ramifications through the muscle provide pathways for regeneration. More complete reinnervation of the muscle is thus insured than when the insertion is made elsewhere.

Another technique was also used in crossing the nerves in which the cut end of the foreign nerve instead of being inserted directly into the muscle, was sutured to the distal stump of the original nerve. The sutures were tubulated in a small piece of artery obtained from another rat according to the method of Weiss ('41). The artery itself was sufficient to hold the two cut ends of nerve together provided a little slack was allowed in the length of nerve. Extra length when needed was obtained by separating the muscular branch from the main trunk farther proximally after removing the common connective tissue sheath. In anticipation of the operation for muscle transposition to be made on some of the cases after regeneration of the crossed nerves, the nerves were

cross-sutured to the lateral head of the gastrocnemius muscle which is more easily transposed than the medial head.

In a number of the first trials ankylosis of the joint set in before muscular activity was restored by nerve regeneration. It was found preferable to leave the deep plantar flexor muscles intact in the first operation and excise them in a second operation after regeneration of the crossed nerves had taken place. Contraction of the deep plantar flexor muscles maintains the mobility of the joint and helps prevent ankylosis.

The operations were performed under sodium amytal anesthesia with a single lateral incision from above the knee to the ankle. A short incision along the medial side of the tibia bone under ether anesthesia was made for removal of the deep plantar flexor muscles in the second operation.

RECOVERY

After the operation the foot hung limply in those cases in which all the extra muscles had been excised. After a period, varying in different cases from 3½ to 6 weeks, active foot movement began to reappear in the operated limbs. This movement from the start was in reverse. Plantar flexion instead of the normal dorsi-flexion occurred in the withdrawal reflex. When the rats tried to rise upright on their toes, the foot was dorsi-flexed instead of plantar-flexed so that the toes swung up in the air and the body weight fell on the back point of the heel. The reversed action gradually became stronger and occurred regularly in all reflex and spontaneous leg movements.

In the remaining cases the deep plantar flexor muscles were excised at the end of 8 weeks. These rats began to move the foot in reverse a few days after the second operation, as soon as the leg had healed.

Ten successful cases were obtained with complete reversal of hind foot movement unrestricted by ankylosis. In eight of these cases, six unilateral, two bilateral, the nerves had been inserted directly into the muscles. In the remaining two, both

unilateral, the nerves had been cross-sutured in arterial tubes. Two more successful cases were obtained in which the muscles had been transposed 8 weeks after the nerves were cross-sutured. The muscles were transposed and the tendons re-inserted in such position that contraction of the gastrocnemius muscle produced dorsi-flexion of the foot instead of the normal plantar flexion, and contraction of the anterior tibial muscle produced plantar flexion instead of dorsi-flexion. In these animals the reversal of muscle action cancelled the reversal produced by nerve crossing, so that dorsi-flexion and plantar flexion occurred in normal phase in all active leg movement. The twelve cases at the time the nerves were crossed varied in age from 40 to 250 days. No age difference appeared in the results except that there was some indication of more rapid and complete nerve regeneration in the younger animals.

The animals were kept under close observation in large cages with a deep flooring of sawdust to protect the operated feet. Once a week for the first 2 weeks and monthly thereafter, the animals were put through a series of twelve specific test reactions involving plantar flexion and dorsi-flexion of the foot. These reactions included the suspended and supporting phases of locomotion and climbing, the withdrawal reflex, placing reaction, scratch reflex, rising upright on the hind legs, escape movements when the rat is held down on its back by pressing across the abdomen, and braking movements of the hind feet when the rat is pulled forward across the floor by its forequarters. These test reactions furnish a reliable index of the contraction of the shank muscles in both voluntary and reflex activity. They have been described in detail with the corresponding foot movements in normal and in reverse phase (Sperry, '40). Moving pictures of some of the test reactions taken 3 weeks after the appearance of reversed foot movement were compared with pictures of the same reactions taken 1 year later.

RESULTS

Cases tested for modulation of nerve by muscle. Six of the unilateral nerve cross cases were left till their deaths without

further treatment. They were kept 6, 10, 13, 15 and 18 months after the operation, respectively. No adjustment in foot movement appeared. The reversal was fully as vigorous and consistent just before death as at the beginning. Likewise no change occurred in those two special cases in which the muscles supplied by the crossed nerves had also been transposed. Flexion and extension of the foot continued in the normal phases of leg coordination. The foot movements, though slightly weakened by incomplete reinnervation, were very similar to those in controls in which all muscles of the shank had been removed except the lateral gastrocnemius and the anterior tibial. There had been no sign of a shift back toward reversal of foot movement when they were sacrificed 15 months after the operation.

The results in regard to nerve modulation in these cases are clear and may be dispensed with briefly. Modulation of nerve by muscle obviously does not occur in rats of 40 days or older. The motor nerves, already specifically determined by their original muscles, are no longer in a sufficiently labile condition to be respecified by foreign muscles. Consequently, in connection with the problem of possible restoration of function after nerve crossing, modulation of nerve by muscle may be discounted as a factor operating in rats at this age.

Cases in which reeducation was attempted. The reversal of foot movement which follows nerve crossing is quite similar in all respects to the reversal which follows muscle transposition. The factors involved in reeducation after crossing nerves should be very much the same as after transposing the muscles activated by those nerves. It was thought, however, that because the position of the muscles is not changed by nerve crossing the array of proprioceptive and kinesthetic stimuli might possibly be more favorable for reeducation after nerve crossing than after muscle transposition. The two-joint gastrocnemius muscle with its origin on the femur bone is mechanically stretched in normal phase by movement of the knee joint. This normal stretching of the muscle is, in most responses, simply exaggerated after nerve crossing by the reversal of foot movement, whereas such mechanical effects of knee action were completely abolished in the muscle transposition experiments by attaching the origin of the gastrocnemius muscle to the tibia bone.

With the purpose of forcing out reeducational correction if possible, special treatment was administered to four cases, two unilateral and two bilateral, in which as indicated by palpation, full reinnervation of the muscles had taken place. In the two unilateral cases the contralateral hind foot was immobilized in a neutral position of slight dorsi-flexion by operations causing adhesions and ankylosis of the joint. Four weeks after the appearance of reversed movement, the front legs of one unilateral and one bilateral case were amputated at the shoulder. Because this operation made the animals entirely dependent on the hind legs for support and for locomotion and provided a continuous condition of training where the alteration demanded for the animals' well-being involved the simple sustained contraction of one muscle and inhibition of its antagonist, this test was considered crucial of the rats' ability to correct by a learning process the reversed foot movement. When these rats tried to support themselves on their hind feet, contraction of the anterior tibial muscle activated by the soleus nerve produced dorsi-flexion of the foot so that the toes and sole of the foot were lifted up in the air. The rats continued to balance and hobble about awkwardly on the back points of their heels with the toes pointing upward. They never learned to bring the toes and ball of the foot down to the floor and use them for support. Forty-nine and 63 days of age at the time of the first operation when the nerves were crossed, these two cases died 17 and 16 months, respectively, after amputation of the front legs without any sign of reeducation.

The other two cases, 40 and 83 days old at the time of the first operation, were compelled to rise upright on their hind legs to obtain food. Hard food which could be gnawed only a small bit at a time from a self-feeder was gradually raised so high that it was almost out of reach. When the rats stretched upright to reach the food, their feet were dorsi-flexed

so that they could not get up off their heels. By straining upward to their utmost they were able only to barely nibble at the food. The animals were watched to see if they would learn to contract the gastrocnemius on rising upright, as rats do normally, and thus raise themselves to a position from which the food would be more accessible. They continued to struggle and strain to reach the food from the back points of their heels without ever learning to contract the gastrocnemius muscle at the correct time or even to inhibit contraction of the anterior tibial muscle which kept the toes and ball of the foot in the air and prevented use of the flat of the foot as an aid in balancing. At the end of 6 months the animals had become quite thin and training was discontinued. Up to the time of their deaths 10½ and 9 months later, the reversal of foot movement persisted without modification. In being unable to correct or even to inhibit the reversal of foot movement which was more of a hindrance to them than no foot movement at all, these rats in which the muscles had been left in normal position and only the nerves crossed, were entirely similar to those previous cases in which the muscles had been transposed.

Checks and controls. Post-mortem dissection showed that nerve regeneration had been as intended. There were no stray fibers to the muscles from the original nerve stumps or from other foreign nerves. In two cases which were showing signs of senility and were ready to be sacrificed, the peroneal and tibial nerves were cut and the distal ends stimulated electrically above the point at which the nerves had been sutured. Stimulation of the peroneal nerve caused strong contraction of the gastrocnemius muscle and none of the anterior tibial muscle, while stimulation of the tibial nerve caused strong contraction of the anterior tibial muscle and none of the gastrocnemius muscle. Since the gastrocnemius muscle is normally supplied by the tibial nerve and the anterior tibial muscle by the peroneal nerve, these physiological tests also showed that nerve regeneration had taken place as intended.

The incision was then closed in one of these cases and the anesthesia removed. After healing, 1 week later, it was obvious that the reversal of foot movement had been completely abolished by cutting the nerves. In an extra case in which the operation had not been successful because the reversed movement occurred only in the plantar direction, dorsi-flexion being absent, dissection revealed that the nerve crossed to the anterior tibial muscle had pulled loose, the nerve to the gastrocnemius muscle remaining intact. From this evidence there was no doubt that the reversed foot movement was caused by active contraction of the muscles to which the nerves had been crossed and not by any extraneous mechanical factors.

In control animals in which all the shank muscles had been removed except the anterior tibial and medial gastrocnemius muscles, these two muscles were strong enough to allow the foot to be used to good advantage in coordination very close to that of the normal rat. Two controls similar to the above except that the nerves were cut and connected again to their original muscles in one case and to muscles of the same action in the other, in the former by suture and in the latter by direct insertion, also showed good coordination in normal phase.

In the experimental group reinnervation of the anterior tibial muscle was sufficient in all cases to cause good strong dorsi-flexion of the foot against gravity. That reinnervation of the gastrocnemius muscle was sufficient to lift the body weight of the rat off its heels was questionable in three cases since at death the muscles were only about one-quarter normal size. In the remainder of the cases reinnervation was more complete and in the cases in which reeducation was attempted, palpation previous to training and post-mortem dissection and weighing indicated no appreciable loss of muscle mass. Strong plantar flexion of the foot in the reverse phase was present in all cases.

That sensory as well as motor nerves had regenerated into the foreign muscles was shown by the fact that pinching the exposed muscles under light anesthesia with a blunt forceps produced reflex responses. Reflex responses elicited by prick-

ing the skin and pulling the hair over all regions of the shank, ankle, and foot, and to flexing the toes and ankle about a month after return of function showed that the operation had not impaired the sensitivity of the limb.

CROSSES BETWEEN PERONEAL AND TIBIAL NERVES

Since regeneration of nerves is unselective (Weiss, '36), the crossing of large nerve trunks such as the peroneal and tibial must result in a random redistribution of the motor fibers of any one muscle of the shank or foot to a large number of foreign muscles. Likewise any one foreign muscle must be reinnervated by a heterogeneous lot of fibers that originally were spread among many different muscles. A similar random dispersal must occur among the sensory fibers. For reeducation or reflex regulation to occur in the face of such confused reinnervation would imply an extreme plasticity, homogeneity, and adaptability on the part of the nerve centers that is directly negated by the results of muscle transposition and nerve crosses between individual muscular nerve branches. The latter results show that contraction of the shank muscles as a group cannot be dissociated in the nerve centers from that of the rest of the leg musculature. It seems improbable that this same dissociation plus the much finer dissociations between different groups of shank and intrinsic foot muscles and even between individual neurons, as would be required after unselective regeneration of the peroneal and tibial nerve trunks, could be made after crossing these nerves. Learning would be simpler presumably after reconnecting the fibers of one muscle directly to another single muscle. However, since reeducational adjustment has been reported to follow the crossing of the compound peroneal and tibial nerve trunks in dogs by Osborne and Kilvington and in dogs, cats, rabbits, and pigs by Rawa, this operation also was performed on a number of rats.

Anatomically the dorsi-flexor muscles of the foot are supplied by the peroneal nerve and the plantar flexors by the tibial nerve. In the normal rat electrical stimulation under

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light anesthesia of the distal cut end of the peroneal nerve causes sharp strong dorsi-flexion of the foot. Likewise, stimulation of the tibial nerve causes vigorous clear-cut plantar flexion of the foot.

Twenty cases were prepared. They were operated at ages ranging from 15 to 80 days. After cutting the nerves the proximal end of the peroneal was sutured to the distal end of the tibial and the proximal end of the tibial to the distal end of the peroneal. The sutures were enclosed in artery tubes and, because the nerve trunks lie side by side, a long sheet of beef allantoic membrane (Bauer and Black's "insultoic membrane") was placed between the sutured nerves to prevent cross regeneration of fibers to their original branches.

Regeneration occurred as intended. When the legs were reopened after 2½ months, the two nerve trunks were distinctly separable with no sign of stray fibers crossing from one suture to the other. The shank muscles had regained their full size. After cutting the nerve trunks proximal to the point of suture in three cases, electrical stimulation of the cut ends produced dorsi-flexion when the crossed tibial nerve was stimulated, and plantar flexion when the crossed peroneal nerve was stimulated. Clearly the mass of structures normally supplied by the tibial fibers had been reinnervated by the peroneal fibers, and vice-versa.

Flaccid paralysis with muscular atrophy immediately followed the operation. On regeneration of the nerves with resultant recovery of muscular strength and tonus, the foot was moved abnormally but not in reverse as after crosses between individual muscles. There were no loose free reciprocal movements of the foot. Active dorsi-flexion was never seen. Only when the rats were at rest with the leg muscles relaxed did the foot attain a normal position of dorsi-flexion, passively flexed underneath the animals by the body weight. Whenever leg movement occurred, the foot was held rather stiffly and moved only through varying degrees of plantar flexion. As time went on, the plantar flexion became more predominant. During activity the foot was kept stiffly extended. In the supporting

phase of locomotion the body weight was supported on the digits instead of on the sole of the foot. The result of this rigid plantar flexion in locomotion was to make the leg coordination of the rats similar to that of digitigrade mammals such as the cat, dog and pig. In the rat, however, the toes are long and become permanently curled after the operation so that the rats walked on the dorsal rather than on the plantar surface of the toes.

The reason for the predominance of plantar flexion with curling of the toes and rigidity of the ankle joint is not entirely clear, though the following factors are probably in part responsible. The peroneal and tibial trunks contain, besides fibers to the directly opposed flexor and extensor muscles, fibers to the peroneal group of muscles and to the group of deep flexor muscles and also to all the small muscles intrinsic to the foot which groups probably do not all function in perfect synchrony with the primary plantar and dorsi-flexors. If, for example, the posterior tibial and the short and long peroneal muscles contract during plantar flexion as they apparently do in man (Wright, '28), then, after crossing their fibers along with those of the dorsi-flexors into the plantar flexor muscles, one would expect to get a continuous plantar-flexor contraction persisting through both phases of locomotion. Also, because the plantar flexors are much more powerful than the dorsi-flexors, any generalized pull on all muscles produced by prolonged contraction, contracture, or even by muscle tonus, after disruption of the myotatic reflex mechanisms for controlling that tonus, would tend to result in predomination of plantar flexion. Whether cause or result, there was an anatomical shortening of the plantar flexor muscles. This shortening was not so severe in the majority of cases as to prevent reeducational adjustment since good dorsi-flexion of the foot could be obtained by electrical stimulation of the nerve. In most of those cases operated at about 15 days of age, however, when growth is still very rapid, the condition became so severe that complete dorsi-flexion was impossible even by forcible manipulation.

The leg coordination following the crossing of peroneal and tibial nerves was quite similar in all twenty rats save for the age difference mentioned above. Fifteen of the animals were kept longer than a year, nine of them as long as 18 months after the operation. Foot movement remained abnormal to the end with no evidence of correction.

One must conclude either that the nervous system of cats, dogs, rabbits, and pigs is considerably more efficient in regard to reeducation than that of rats, which seems very unlikely particularly in the case of pigs whose central nervous system is decidedly more primitive (Kappers, Huber and Crosby, '36), or that the adjustment observed in these other animals was actually due to anatomical and mechanical peripheral effects rather than to central adjustment. In this regard it should be noted that passive extension of a dog's, cat's, rabbit's, or pig's knee mechanically forces an extension of the foot because of the pronounced two-joint action of the plantar-flexor muscles. Dorsi-flexion is mechanically impossible with the knee extended and can occur only, as it does normally, when the knee is flexed. After crossing peroneal and tibial nerves, knee movement which is unaffected by the operation would thus tend on regeneration of the nerves to control foot movement mechanically as the two-joint muscles gradually recovered their strength and tonus. The effects observed after crossing the peroneal and tibial nerves in the rat, obviously not normal in this animal, would be functionally very adaptive in a short-toed digitigrade animal, and might easily be mistaken for a restoration of normal coordination.

There was no indication of nerve modulation in these cases. Unfortunately the effect of modulation of the few fibers that had not yet reached their end-organs at the time of operation in the youngest animals would have been so weak that it would have been overshadowed by the action of the fibers already established.

CONCLUSION

No adaptive functional adjustment of the nervous system took place in these rats after the connections from the spinal

centers to antagonistic limb muscles had been exchanged. The crossing of the peroneal and tibial nerves and the crossing of the pure muscular branches of these nerves resulted in an awkward and thoroughly abnormal foot movement in the former case and in a complete reversal of foot movement in the latter, neither of which was ever corrected by automatic reflex regulation or by a gradual learning or conditioning process. These results are in agreement with those of Cunningham (1898) who crossed the median and ulnar nerves in dogs and stood alone in maintaining that recovery of normal muscular coordination does not follow the crossing of limb nerves. They indicate that the more numerous reports implying a surprising plasticity and regulatory adaptability of the central nervous system to disarrangements of the normal peripheral relations are not to be accepted without question, and show in contrast an extremely unplastic fixation of the basic motor patterns for hind limb coordination.

Persistence of the original patterns of discharge to the limb musculature after peripheral alterations that thoroughly disrupted the normal array of afferent stimuli from the limb supports the contention that the control of limb coordination is in large part central. As pointed out by Gray ('39), peripheral stimuli are extremely important in the timing of limb responses, in controlling the intensity of limb responses, and in determining in many cases which of various possible limb responses as wholes will be set off. But since the elementary patterns of limb coordination persist in the rat after extreme distortion of peripheral conditions produced by nerve crossing, muscle transposition, and even complete deafferentation of the limb; the organization of the intrinsic motor patterns themselves must depend primarily on central rather than peripheral factors.

Permanent retention of the original incidence of discharge of the motor nerve fibers after their regeneration into foreign antagonistic muscles also demonstrates that nerve cells in juvenile and adult stages of the rat are no longer in a sufficiently labile condition to be respecified by foreign muscles.

In amphibians where modulation of nerve by muscle has been most thoroughly studied it has been shown that in larval stages respecification takes place quite readily, while in newly metamorphosed toads it occurs only very slowly (Weiss, '36, p. 516), and in fully grown toads the capacity of nerve cells to undergo modulation is completely lost (Weiss, unpublished). Mammalian tissues in general are less labile than those of amphibians and their nerves probably become irreversibly determined in an earlier stage of development soon after reaching the muscles.

The results in the rat are not necessarily contradictory to the results in larval amphibians in their implications regarding the role of inter-neuron connections in reflex activity and central nervous function. Nerve modulation may be considered an embryological inductive influence which affects development of the central connections of motor cells in the cord rather than a factor which selectively modifies the nerves' sensitivity to central excitatory agents. According to this interpretation, the formation of synaptic terminations on motor cells by the telodendria of internuncial neurons is conditioned by the specific biochemical properties induced in the different motor cells by their muscles. End-organ connection formed by outgrowing nerve fibers in ontogeny becomes, on this basis, an important factor in the laying down and differentiation of central reflex relations. The influence of peripheral organs on the quantitative development of the central nervous system has already been well demonstrated (see Detwiler, '36).

After crossing peripheral nerves, one would expect a restoration of normal function due to modulation of nerve by muscle, according to this interpretation, only in cases where the peripheral nerves had not already become irreversibly determined by their original end-organs and where the central nervous system was still in a sufficiently labile condition to permit compensatory growth readjustments in the central connections and also where the central terminations of the nerves crossed were located in the same region of the central

nervous system. At present there is no crucial evidence to indicate whether modulation affects the selective sensitivity of the motor neurons or the central connections of these neurons. But because this alternative explanation of the phenomenon of homologous response is consistent with both the amphibian and mammalian experiments and also with the classical conceptions of central nervous physiology it is mentioned here as a working hypothesis.

SUMMARY

1. In ten rats (eight unilateral and two bilateral cases, operated at ages ranging from 40 to 250 days) exchanging the nerve connections of flexor and extensor muscles in the shank produced a reversal of foot movement.

2. In all ten cases the foot movement remained fixedly reversed to the end with no corrective modification whatever. Seven cases were kept longer than 15 months after the operation. Immobilization of the contralateral hind foot, training the rats to rise upright on their hind legs for food, and amputation of both front legs at the shoulder all failed to induce reeducation.

3. Post-mortem examination and physiological tests showed that nerve regeneration had been as intended, that sensitivity of the shank and foot had not been impaired by the operation, and that sensory as well as motor fibers had reinnervated the muscles. Severance of the crossed nerves abolished the reversed movement. Control animals, similarly operated except that the nerves were reconnected to the original muscles, showed foot movement in normal phase in all activity.

4. In two additional rats, both unilateral; transposition of flexor and extensor muscles after the nerves to these muscles had previously been crossed resulted in foot movement in normal phase. No change toward reversal occurred after 15 months.

5. In twenty rats, ranging in age from 15 to 80 days, the peroneal and tibial nerves were crossed instead of the single nerve branches to individual muscles. This operation pro-

duced an abnormal limb coordination characterized by indiscriminate contraction of the shank muscles and a predomination of plantar flexion of the foot. This abnormal coordination persisted for 18 months without any sign of a central nervous adjustment.

6. The results furnish new evidence of the rigid organization in the rat of the basic motor patterns for hind limb coordination. They also show that, in a mammal, motor nerve cells in post-embryonic condition do not have the capacity to undergo muscle-specific modulation after regeneration into foreign muscles.

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